

Trimethylsilylnitrate: a useful reagent for direct synthesis of 2-deoxy-*O*-glycosides from glycols[§]

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This paper is respectfully dedicated to Prof. P.T. Narasimhan
on the occasion of his 75th birthday

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Abstract: Trimethylsilylnitrate acts as a useful reagent for the addition of alcohols to glycols forming 2-deoxy-*O*-glycosides in good to excellent yields.

Keywords: 2-Deoxy-*O*-glycosides, trimethylsilylnitrate, glycols, ClSiMe₃, AgNO₃

Introduction

2-Deoxy-*O*-glycosides are integral parts of many prominent biologically active natural products² such as aureolic acids,³ cardiac glycosides⁴ and antitumor agents such as calicheamycin.⁵ In view of this, many synthetic methods have been developed for the stereoselective synthesis of α or β -2-deoxy-*O*-glycosides. Although, synthesis of 2-deoxy-*O*-glycosides from 2-deoxysugars bearing a leaving group at the anomeric centre is well known, control of the stereochemistry of the *O*-glycosidic bond is somewhat difficult because of the lack of a stereodirecting substituent at C-2. The leaving groups at the anomeric centre include halides,^{6a,b} thioglycosides,^{6c} n-pentenyl glycosides,^{6d} trichloroacetimidates,^{6e} sulfoxides,^{6f} phosphites,^{6g} and phosphoramidites.^{6h} These methods, however, need prior preparation of 2-deoxysugars with a desired leaving group at the anomeric centre. Additionally, iodoglycosylation of glycols using iodonium dicollidine perchlorate (IDCP)^{7a,b} or ceric ammonium nitrate (CAN)-NaI^{7c,d} are other methods reported in literature but they require reductive de-iodination in the next step to obtain 2-deoxy-*O*-glycosides. Apart from this, direct addition of alcohols to glycols catalyzed by a protic acid (MeOH·HCl,^{8a} cation-exchange resin AG 50 WX₂,^{8b} Ph₃P·HBr^{8c}) or a Lewis acid (BBR₃ or BCl₃^{9a} and CeCl₃·7H₂O-NaI^{9b}) has also been reported for this purpose. One of the problems, however, in these direct glycosylations is the possibility of the Ferrier reaction and hence not all

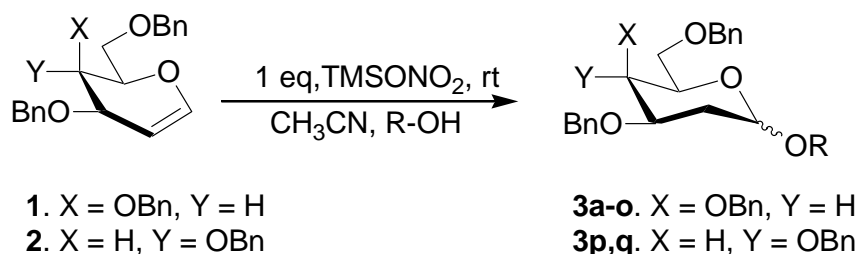
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the protic or Lewis acids are suitable for this purpose. Nevertheless this one pot procedure is useful and hence more recently a polymer-bound Lewis acid¹⁰ has also been employed for the synthesis of 2-deoxy-*O*-glycosides.

Results and Discussion

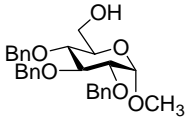
Recently we have reported a CAN catalyzed transformation of glycols to 2-deoxy-*O*-glycosides under mild conditions.¹¹ As part of our ongoing programme^{11,12} to develop newer methods in functionalizing glycols towards obtaining useful carbohydrate intermediates, we have now found that trimethylsilylnitrate (TMSONO₂), readily made from ClSiMe₃ and AgNO₃, works as a useful reagent for the synthesis of 2-deoxy-*O*- glycosides. TMSONO₂ has been used¹³ in conjunction with BF₃·Et₂O as a source of NO₂⁺ for nitration of aromatics.



Scheme 1

We have reported¹⁴ its use along with CrO₃ to convert olefins into α -nitroketones and in converting cyclic ethers into lactones. More recently, we have found¹ that TMSONO₂ along with Me₃SiN₃ converts glycols into the corresponding 2-deoxy-1-glycosyl azides which, in turn, can be converted into 2-deoxy- β -1-*N*-glycopeptides. In an effort to explore the potential of TMSONO₂, we report in this paper that TMSONO₂ permits addition of alcohols to glycols forming 2-deoxy-*O*-glycosides in good to excellent yields at room temperature in 2-5 h. A wide variety of alcohols were added on to glycols in the presence of 1 eq. of TMSONO₂. Initial experiments were performed using catalytic amount of TMSONO₂, however, the glycols were found to be largely unreacted. Our results are summarized in Table-1. In all the cases, α -isomer was found to be the major product and in some cases, with a galactal derivative **1** (Scheme 1), it was the exclusive product(entries 1, 2, 11). A disaccharide (entry 14) was also made using this method with galactal **1**, although the yield was moderate. When we used compound **2** (a glucal derivative) under the same reaction conditions, we observed formation of a trace amount of the Ferrier product along with 2-deoxy-*O*-glycosides (entries 16, 17).

Table 1

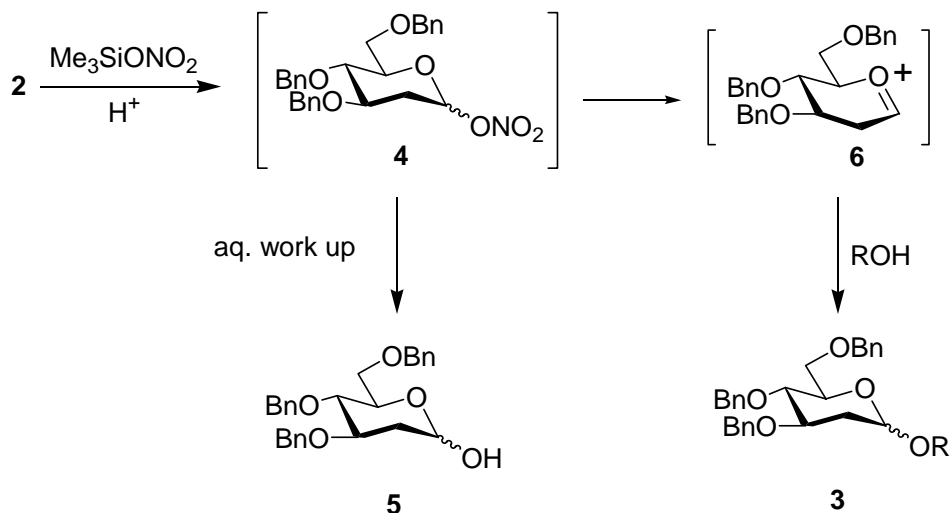
Entry	Glycal	Acceptor	Product 3	Yield %	Time (h)	$\alpha:\beta$
1	1	Methanol	a ¹¹	85	2	α only
2	1	t-Butanol	b ¹¹	52	5	α only
3	1	Isopropyl Alcohol	c ¹¹	83	3	90:10
4	1	Propargyl Alcohol	d	95	3	91:9
5	1	Cinnamyl Alcohol	e	89	3	90:10
6	1	Benzyl alcohol	f ¹¹	85	3	80:20
7	1	Homo propargyl Alcohol	g	90	3	90:10
8	1	3-Bromo-1-propanol	h	92	3	91:9
9	1	Tetrahydrofurfuryl alcohol	i	84	3	90:10
10	1	Cyclohexanol	j ¹¹	80	4	90:10
11	1	Allyl alcohol	k ¹¹	81	3	α only
12	1	Cholesterol	l ¹¹	68	4.5	81:19
13	1	1-Octanol	m	88	3.5	96:4
14	1		n ^{6h,11}	38	4	92:8
15	1	3-Methyl-but-3-en-1-ol	o	92	3	80:20
16	2	Methanol	p ^{6i,11}	80	2	(70:30) ^a ,55:45 ^b ,90:10 ^c
17	2	t-Butanol	q ^{6i,11}	50	4.5	(71:29) ^a ,74:26 ^b ,65:35 ^c

^a Ratio of 2-deoxy-*O*-glycoside and the Ferrier product. ^b $\alpha:\beta$ ratio of 2-deoxy-*O*-glycoside.

^c $\alpha:\beta$ ratio of the Ferrier product.

With regards to the mechanism of this reaction, we suggest that 2-deoxy-*O*-glycosides are formed via the corresponding nitrate esters **4** (Scheme 2) by the nucleophilic displacement by alcohols under acidic reaction conditions.¹⁵ Evidence to this effect was gathered from the following observations. Exposure of a solution of 3,4,6-tri-*O*-benzyl-D-glucal **2** in acetonitrile to

Me₃SiONO₂ (1:1 molar equiv) only, followed by analysis of the reaction mixture by thin-layer chromatography showed a polar spot compared to the starting material. Evaporation of solvent under vacuum gave a product which showed in its IR spectrum a strong peak at 1680 cm⁻¹, whereas its ¹H NMR spectrum showed peaks of no specific splitting patterns NMR spectrum. Mass spectral analysis using electrospray technique (+ ion) suggested the presence of 1-hydroxy sugar derivative **5**, however, the -ve ion detection indicated the presence of a peak at *m/z* 479 corresponding to the nitrate ester **4**.



Scheme 2

Further, if the reaction was worked up before the addition of alcohols then the only product that could be isolated was 2-deoxy-3,4,6-tri-*O*-benzyl-D-glucose **5**. It is, therefore, likely that the product of the reaction between a glycal and TMSONO₂ is a nitrate ester of type **4** which is relatively unstable and gets hydrolyzed to compound **5**. This is not unexpected, since it is known¹⁶ that anomeric nitrates are susceptible towards hydrolysis on column chromatography. Thus, it is fair to assume that the nitrate esters **4** are formed as intermediates in these reactions and then they are subsequently converted to the corresponding 2-deoxy-*O*-glycosides **3** by treatment with glycosyl acceptors viz. the alcohols. Further, we presume that the nitrate esters **4** are first converted to the corresponding oxocarbenium **6**, under the slightly acidic experimental conditions, before reacting with the glycosyl acceptors. This is in view of the fact that the *O*-glycosides formed are predominantly α in nature, resulting from the dominant anomeric effect.

In conclusion, we have found that TMSONO₂ is a new reagent for the synthesis of 2-deoxy-*O*-glycosides in a high stereoselective manner from glycals, and we hope that this methodology will be useful in organic synthesis.

Experimental Section

General Procedures. To a stirred solution of a glycol (0.240 mmol) in CH₃CN (2 mL) at room temperature, were added an alcohol (0.268 mmol) and trimethylsilylnitrate¹³ (0.240 mmol). The reaction mixture was stirred for the time indicated in Table-1. After completion of reaction it was extracted with ethyl acetate (2 x 10 mL) and the usual work-up gave a crude product which was purified by column chromatography to give a pure product which was characterized by spectroscopic and analytical means.

Selected data: propargyl 3,4,6-tri-*O*-benzyl-2-deoxy- α/β -D-lyxo-hexopyranoside (3d). Yield: 95%, liquid. $[\alpha]_D^{25} = +59.5$ (*c* 2.15, CH₂Cl₂). IR (CH₂Cl₂) ν_{\max} : 3300, 2119, 1162, 1065 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.0-2.05 (dd, *J* = 13.0, 4.4 Hz, 1H, H-2), 2.22-2.29 (dt, *J* = 12.6, 3.8 Hz, 1H, H-2'), 2.36 (t, *J* = 2.4 Hz, 1H, -C \equiv C-H), 3.53-3.58 (m, 2H, H-6, H-6'), 3.87-3.93 (m, 3H, H-3, H-4, H-5), 4.16 (t, *J* = 2.4 Hz, 2H, -OCH₂-C \equiv C), 4.40-4.49 (q, *J* = 11.7 Hz, 2H, -OCH₂Ph), 4.59 (br. s, 2H, -OCH₂Ph), 4.63 (d, *J* = 11.7 Hz, 1H, -OCH₂Ph), 4.93 (d, *J* = 11.7 Hz, 1H, -OCH₂Ph), 5.14 (br. d, *J* = 3.1 Hz, 1H, H-1), 7.23-7.35 (m, 15H, aromatic). ¹³C NMR (100 MHz, CDCl₃): δ 30.7, 54.0, 69.2, 70.2, 70.3, 72.7, 73.3, 74.2, 74.4, 79.3, 96.5, 127.1-138.7 (m, aromatic). MSES⁺: 490 [M + NH₄]⁺. Anal. Calcd for C₃₀H₃₂O₅ (472.25): C, 76.25; H, 6.83. Found: C, 76.31; H, 6.88. Characteristic signals for *b*-anomer: ¹³C NMR: δ 32.4, 54.9, 69.0, 70.9, 71.4, 79.1, 97.6, 137.8, 138.1, 138.6.

Cinnamyl 3,4,6-tri-*O*-benzyl-2-deoxy- α/β -D-lyxo-hexopyranoside (3e). Yield: 89%, liquid. $[\alpha]_D^{25} = +16.0$ (*c* 2.5, CH₂Cl₂). IR (CH₂Cl₂) ν_{\max} : 1495, 1097, 1060 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.02-2.06 (br. dd, *J* = 12.6, 3.4 Hz, 1H, H-2), 2.22-2.29 (dt, *J* = 12.4, 3.68 Hz, 1H, H-2'), 3.54-3.65 (m, 2H, H-6, H-6'), 3.93-3.98 (m, 3H, H-3, H-4, H-5), 4.09-4.14 (dd, *J* = 12.8, 6.7 Hz, 1H, -OCH-CH=CH-Ph), 4.26-4.30 (dd, *J* = 12.8, 5.7 Hz, 1H, -OCH'-CH=CH-Ph), 4.40-4.52 (q, *J* = 11.7 Hz, 2H, -OCH₂Ph), 4.60 (br. s, 2H, -OCH₂Ph), 4.62 (d, *J* = 11.5 Hz, 1H, -OCH₂Ph), 4.93 (d, *J* = 11.5 Hz, 1H, -OCH₂Ph), 5.10 (br. d, *J* = 3.1 Hz, 1H, H-1), 6.24-6.31 (m, 1H, -OCH₂-CH=CHPh), 6.57 (br. d, *J* = 15.8 Hz, 1H, -OCH₂-CH=CHPh), 7.21-7.37 (m, 20H, aromatic). ¹³C NMR (100 MHz, CDCl₃): δ 31.1, 67.6, 69.6, 69.9, 70.4, 72.9, 73.4, 74.2, 74.7, 97.1, 125.5, 126.4-128.5 (m, aromatic), 132.6, 136.6, 138.0, 138.4, 138.8. MSES⁺: 568.2 [M + NH₄]⁺. Anal. Calcd for C₃₆H₃₈O₅ (550.68): C, 78.52; H, 6.96. Found: C, 78.58; H, 6.93. Characteristic signals for *b*-anomer: ¹H NMR: δ 4.58-4.60 (dd, *J* = 10.0, 3.8 Hz, 1H, H-1). ¹³C NMR: δ 32.7, 99.0.

Homo propargyl 3,4,6-tri-*O*-benzyl-2-deoxy- α/β -D-lyxo-hexopyranoside (3g). Yield: 90%, liquid. $[\alpha]_D^{25} = +40.0$ (*c* 1.3, CH₂Cl₂). IR (CH₂Cl₂) ν_{\max} : 3293, 2118, 1162, 1096 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.94 (t, *J* = 2.6 Hz, 1H, -C \equiv C-H), 1.99-2.03 (m, 1H, H-2), 2.19-2.26 (dt, *J* = 12.6, 3.6 Hz, 1H, H-2'), 2.42-2.47 (dt, *J* = 7.0, 2.6 Hz, 2H, -OCH₂-CH₂-), 3.53-3.63 (m, 3H, H-6, H-6' and -OCH-CH₂-), 3.69-3.75 (m, 1H, -OCH'-CH₂-), 3.89-3.96 (m, 3H, H-3, H-4, and H-5), 4.40-4.51 (q, *J* = 11.9 Hz, 2H, -OCH₂Ph), 4.59 (br. s, 2H, -OCH₂Ph), 4.62 (d, *J* = 11.7 Hz, 1H, -OCH₂Ph), 4.93 (d, *J* = 11.7 Hz, 1H, -OCH₂Ph), 5.01 (br. d, *J* = 2.9 Hz, 1H, H-1), 7.22-7.34

(m, 15H, aromatic). ^{13}C NMR (100 MHz, CDCl_3): δ 19.7, 31.0, 65.4, 69.2, 69.4, 69.9, 70.4, 72.8, 73.4, 74.2, 74.7, 81.3, 97.9, 127.2-128.3 (m, aromatic), 138.1, 138.4, 138.8. MSES^+ : 504 $[\text{M} + \text{NH}_4]^+$. Anal. Calcd for $\text{C}_{31}\text{H}_{34}\text{O}_5$ (486.59): C, 76.52; H, 7.04. Found: C, 76.55; H, 7.10. Characteristic signals for *b*-anomer: ^1H NMR: δ 2.06-2.10 (m, 2H, H-2, H-2'), 4.56-4.59 (dd, $J = 10.0, 2.2$ Hz, 1H, H-1), 4.91 (d, $J = 11.7$ Hz, 1H, $-\text{OCH}_2\text{Ph}$). ^{13}C NMR: δ 20.0, 32.6, 66.9, 70.1, 71.5, 73.4, 74.0, 100.3, 138.0, 138.3, 138.7.

3-Bromo-*n*-propyl 3,4,6-tri-*O*-benzyl-2-deoxy- α/β -D-lyxo-hexopyranoside (3h). Yield: 92%, liquid. $[\alpha]_D^{25} = +24.4$ (c 2.05, CH_2Cl_2). IR (CH_2Cl_2) ν_{max} : 1162, 1096 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.95-1.99 (dd, $J = 12.9, 4.1$ Hz, 1H, H-2), 2.03-2.14 (m, 2H, H_a -2), 2.25-2.26 (dt, $J = 12.7, 3.9$ Hz, 1H, H-2'), 3.43-3.62 (m, 6H, H-5, H-6, H-6', H_a -3 and H_a -1), 3.73-3.78 (m, 1H, H_a -1'), 3.87-3.92 (m, 2H, H-3, H-4), 4.41-4.94 (m, 6H, 3 x $-\text{OCH}_2\text{Ph}$), 4.96 (br. d, $J = 3.1$ Hz, 1H, H-1), 7.23-7.36 (m, 15H, aromatic). ^{13}C NMR (100 MHz, CDCl_3): δ 30.4, 31.1, 32.5, 64.7, 69.4, 69.9, 70.3, 72.8, 73.4, 74.2, 74.6, 97.9, 126.9-128.4 (m, aromatic), 138.0, 138.4, 138.8. MSES^+ : 574 $[\text{M} + \text{NH}_4]^+$. Anal. Calcd for $\text{C}_{30}\text{H}_{35}\text{BrO}_5$ (555.40): C, 64.86; H, 6.35. Found: C, 64.90; H, 6.41. Characteristic signals for *b*-anomer: ^{13}C NMR: δ 30.6, 32.6, 32.7, 66.6, 69.2, 69.6, 70.3, 71.0, 71.5, 73.5, 74.1.

Tetrahydrofurfuryl 3,4,6-tri-*O*-benzyl-2-deoxy- α/β -D-lyxo-hexopyranoside (3i). Yield: 84%, liquid. $[\alpha]_D^{25} = +31.3$ (c 1.15, CH_2Cl_2). IR (CH_2Cl_2) ν_{max} : 1202, 1104 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.50-1.57 (m, 4H, H_a -3, H_a -4), 1.96-2.0 (br. dd, $J = 12.4, 4.6$ Hz, 1H, H-2), 2.18-2.25 (dt, $J = 13.0, 3.8$ Hz, 1H, H-2'), 3.32-3.66 (m, 6H, H_a -1, H_a -5, H-6 and H-6'), 3.81-3.95 (m, 4H, H-3, H-4, H-5 and H_a -2), 4.42 and 4.50 (2d, $J = 11.9$ Hz, 2H, $-\text{OCH}_2\text{Ph}$), 4.59 (br. s, 2H, $-\text{OCH}_2\text{Ph}$), 4.61 (d, $J = 11.5$ Hz, 1H, $-\text{OCH}_2\text{Ph}$), 4.93 (d, $J = 11.5$ Hz, 1H, $-\text{OCH}_2\text{Ph}$), 4.95 (br. d, $J = 3.0$ Hz, 1H, H-1), 7.23-7.34 (m, 15H, aromatic). ^{13}C NMR (100 MHz, CDCl_3): δ 29.3, 29.4, 31.8, 67.4, 69.3, 69.5, 69.7, 70.4, 72.9, 73.4, 74.0, 74.2, 74.9, 97.6, 127.2-138.8 (m, aromatic). MSES^+ : 536 $[\text{M} + \text{NH}_4]^+$. Anal. Calcd for $\text{C}_{32}\text{H}_{38}\text{O}_6$ (518.64): C, 74.11; H, 7.39. Found: C, 74.17; H, 7.45. Characteristic signals for *b*-anomer: ^1H NMR: δ 2.03-2.10 (m, 2H, H-2, H-2'), 4.57-4.59 (dd, $J = 9.7, 2.0$ Hz, 1H, H-1), 4.91 (d, $J = 11.5$ Hz, 1H, $-\text{OCH}_2\text{Ph}$). ^{13}C NMR: δ 26.0, 29.5, 31.2, 100.4, 138.2, 138.8.

3-Methyl-3-butenyl 3,4,6-tri-*O*-benzyl-2-deoxy- α/β -D-lyxo-hexopyranoside (3o). Yield: 92%, liquid. $[\alpha]_D^{25} = +36.5$ (c 1.4, CH_2Cl_2). IR (CH_2Cl_2) ν_{max} : 1603, 1163, 1095 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.71 (s, 3H, $-\text{C}(\text{CH}_3)=\text{CH}_2$), 1.95-2.0 (dd, $J = 12.8, 4.4$ Hz, 1H, H-2), 2.18-2.32 (m, H-2' and $-\text{OCH}_2-\text{CH}_2-$), 3.45-3.64 (m, 4H, H-5, H-6, H-6' and $-\text{OCH}-\text{CH}_2-$), 3.69-3.75 (m, 1H, $-\text{OCH}'-\text{CH}_2-$), 3.88-3.94 (m, 2H, H-3, H-4), 4.40-4.52 (q, $J = 11.7$ Hz, 2H, $-\text{OCH}_2\text{Ph}$), 4.60 (br. s, 2H, $-\text{OCH}_2\text{Ph}$), 4.62 (d, $J = 11.7$ Hz, 1H, $-\text{OCH}_2\text{Ph}$), 4.93 (d, $J = 11.7$ Hz, 1H, $-\text{OCH}_2\text{Ph}$), 4.72 (d, $J = 11.0$ Hz, 2H, $-\text{C}=\text{CH}_2$), 4.97 (br. d, $J = 2.9$ Hz, 1H, H-1), 7.23-7.34 (m, 15H, aromatic). ^{13}C NMR (100 MHz, CDCl_3): δ 22.8, 31.2, 37.6, 65.8, 69.5, 69.8, 70.3, 72.9, 73.4, 74.2, 74.7, 97.6, 111.48, 127.2-138.8 (m, aromatic), 142.8. Characteristic signals for *b*-anomer: δ 22.7, 32.7, 37.5, 67.5, 69.2, 70.1, 71.6, 73.5, 74.0, 74.1, 100.3, 111.42, 142.6. MSES^+ : 520 $[\text{M} + \text{NH}_4]^+$. Anal. Calcd for $\text{C}_{32}\text{H}_{38}\text{O}_5$ (502.64): C, 76.46; H, 7.62. Found: C, 76.49; H, 7.66.

Octyl 3,4,6-tri-*O*-benzyl-2-deoxy- α/β -D-lyxo-hexopyranoside (3m). Yield: 88%, liquid. $[\alpha]_D^{25} = +27.5$ (*c* 1.7, CH₂Cl₂). IR (CH₂Cl₂) ν_{\max} : 1163, 1095 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.83-1.2 (m, 13H, *octyl*), 1.5-1.54 (m, 2H, -OCH₂CH₂-), 1.96-2.00 (dd, *J* = 12.4, 3.6 Hz, 1H, H-2), 2.18-2.25 (dt, *J* = 13.0, 3.6 Hz, 1H, H-2'), 3.32-3.38 (m, 1H, -OCH-CH₂-), 3.54-3.66 (m, 3H, H-6, H-6' and -OCH-CH₂-), 3.89-3.95 (m, 3H, H-3, H-4, H-5), 4.40-4.52 (q, *J* = 11.9 Hz, 2H, -OCH₂Ph), 4.60 (br. s, 2H, -OCH₂Ph), 4.62 (d, *J* = 11.5 Hz, 1H, -OCH₂Ph), 4.93 (d, *J* = 11.5 Hz, 1H, -OCH₂Ph), 4.96 (br. d, *J* = 3.1 Hz, 1H, H-1), 7.23-7.34 (m, 15H, aromatic). ¹³C NMR (100 MHz, CDCl₃): δ 22.6, 26.2, 29.2, 29.3, 29.5, 29.6, 31.2, 31.8, 60.4, 69.5, 69.7, 70.4, 73.0, 73.4, 74.2, 74.9, 97.6, 127-128 (m, aromatic), 138.3, 138.5, 138.9. MSES⁺: 546 [M + NH₄]⁺. Anal. Calcd. for C₃₆H₅₀O₅ (562.78): C, 76.83; H, 8.96. Found: C, 76.88; H, 8.99.

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